- it would have been obvious, at the time the invention was made, to vary the amounts of active agent as well as the amounts of wax present in the formulation of Jang,
- it would have been obvious to include, as the active cores of Jang, the particles taught by Khan, and
- one of ordinary skill in the art would have been motivated to perform the changes in the amount of active agent and the amount of wax and other excipients.

Before discussing in detail the combination of Jang with the newly-cited reference Khan, the applicant will very briefly make reference to the textbook edited by A. Kydonieus, *''Treatise on controlled drug delivery''* (1992) by Marcel Dekker Inc., especially chapter 6 (Oral Controlled-Release Delivery) at pages 284-295, a copy of which is enclosed. This textbook is certainly one which a person of ordinary skill in the art would consider as relevant to the field of the invention.

Within the various categories of continuous release systems (page 284), the textbook considers diffusion-controlled systems (page 290) and teaches that they fall into two basic categories: (1) reservoir devices, and (2) matrix devices.

In reservoir devices, a water-insoluble polymeric material encases (coats) a core of drug, i.e. drug release through the system occurs by partition through the coating membrane, drug penetrates the membrane and diffuses to the other side, and eventually into the dissolution media (page 290). Parameters crucial in maintaining a constant rate of drug release from the reservoir system include polymer ratio in the coating, film thickness and hardness of microcapsules (page 291).

Matrix devices employ a system where the drug is compressed with a slowly dissolving or insoluble polymer, the rate of drug availability being controlled by the rate of penetration of the dissolution medium through the matrix and to the surface of the unit (page 292). Three major types of matrix systems are fatty, plastic, and hydrophilic matrices. Fatty matrices

consist of waxes and are generally prepared by dispersing the drug and excipients in molten wax, followed by congealing and coating (page 295).

In view of the general knowledge represented by this textbook, it will clearly appear that both Jang and Khan relate to matrix devices, whereas the claimed invention relates to a reservoir device.

Jang teaches a controlled release formulation comprising :

- from 0.01 to 95% of a particulate biologically active agent smaller than 10 mesh, and
- from 5 to 99.9% of a controlled release compressible binder mixture (matrix) containing :
  (a) from 0 to 99% of a fatty acid material or neutral lipid powder smaller than 20 mesh,
  (b) from 0 to 99% of a wax powder smaller than 20 mesh, and
  (c) from 1 to 100% of a hydrophobic carbohydrate polymer powder, e.g. ethyl cellulose, smaller than 20 mesh.

According to Jang, the biologically active agent is readily dispersed into the blended powders providing the matrix whereby the resultant formulation can be dry and direct compressed to produce tablets. Thus Jang discloses a matrix device as taught by the textbook of Kydonieus.

Jang teaches a production process (dry powder blending) for the compressible inactive matrix which cannot yield inactive beads as required by claims 39 and 44. Jang does not teach an active portion in the form of coated beads as required by claims 39 and 44. Therefore, Jang cannot encounter a typical problem of reservoir devices, i.e. preventing cracking of the coating of the active portion during tablet compression.

Khan, in order to overcome the disadvantages of certain compositions containing a matrix in the core, teaches dual control release systems comprising :

(a) a core having 60 to 90% of a drug, and 5 to 40% of an edible material having a melting point from 25 to 100°C which may be a natural wax or a microcrystalline wax, and

(b) a porous coating layer over the core,
the weight ratio of the core to the coating layer being from 94 :6 to 98 :2.

The system of Khan is prepared by melting the edible material and drug to form a molten mixture, cooling and milling the said mixture and compressing milled mixture to form tablet core, then coating the tablet core with a coating layer aqueous suspension. The system is then incorporated into a hard or soft confectionery (such as toffee or chewing-gum) further including pharmaceutical carriers.

Khan teaches coating a core including an active portion (drug) and an inactive portion (wax), not providing the inactive portion (wax) apart from the coated active portion as required by claims 39 and 44.

Khan teaches a production process (melting, milling and compressing) for the active core which cannot yield active beads as required by claims 39 and 44. Furthermore, Khan provides the optional pharmaceutical excipients apart from the wax-containing portion, not within the wax-containing portion as required by claims 39 and 44.

Thus, just like Jang, Khan teaches a fatty matrix device as defined by the textbook of Kydonieus. These matrix devices are totally unrelated to the category of reservoir devices to which belongs the present invention.

The purpose of the present invention is, within the context of a reservoir device, to prevent cracking of the coating during compacting.

The solution to that problem as defined by claims 39 and 44 was not obtained by varying the amounts of active agent or the amounts of wax present in the formulations of Jang, or by including the particles of Khan into the active cores of Jang, but by providing a structurally totally different formulation including cushioning wax beads.

A person of ordinary skill in the art would not have been motivated towards the reservoir system defined by claims 39 and 44 by considering a combination of references relating to matrix systems. Neither reference teaches providing the active portion of the tablet in the form of coated beads, as required by claims 39 and 44. Neither reference provides the optional pharmaceutical excipients within the wax-containing portion of the composition as required by claims 39 and 44.

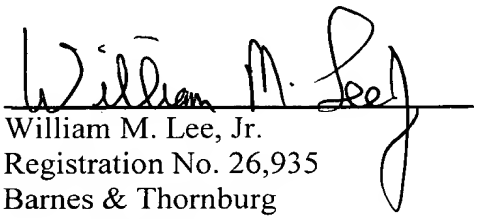
Thus the combination of Jang and Khan does not make obvious the subject matter of claims 39 and 44 or any claim depending therefrom.

Conclusion

This is a very important case to the assignee of the application. In view of the arguments presented therein, favorable reconsideration in the form of a Notice of Allowance is respectfully requested. Should the Examiner not agree or should any matter remain for consideration, an interview is requested and the Examiner is requested to contact the undersigned for that interview.

December 22, 2003

Respectfully submitted,



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